Associations of Neonatal Noncardiac Surgery with Brain Structure and Neurodevelopment: A Prospective Case-Control Study

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Objective To examine the associations of neonatal noncardiac surgery with newborn brain structure and neurodevelopment at 2 years of age.

Study design Infants requiring neonatal noncardiac surgery for congenital diaphragmatic hernia, esophageal atresia, or anterior abdominal wall defect were compared with infants who did not require surgery, matched for sex, gestation at birth, and postmenstrual age at magnetic resonance imaging. Cerebral magnetic resonance imaging was performed at a mean (SD) postmenstrual age of 41.6 (1.7) weeks. Images were assessed qualitatively for brain maturation and injury and quantitatively for measures of brain size, cerebrospinal fluid spaces, and global abnormality. Neurodevelopment was then assessed at 2 years using the Bayley Scales of Infant and Toddler Development, 3rd edition.

Results Infants requiring surgery (n = 39) were 5.9 times (95% CI, 1.9-19.5; $P < .01$) more likely to have delayed gyral maturation and 9.8 times (95% CI, 1.2-446; $P = .01$) more likely to have white matter signal abnormalities compared with controls (n = 39). Cases were more likely to have higher global abnormality scores, smaller biparietal diameters, and larger ventricular sizes than controls. Infants who had surgery had lower mean composite scores in the language (mean difference, −12.5; 95% CI, −22.4 to −2.7) and motor domains (mean difference, −13.4; 95% CI, −21.1 to −5.6) compared with controls.

Conclusions Infants requiring neonatal noncardiac surgery have smaller brains with more abnormalities compared with matched controls and have associated neurodevelopmental impairment at 2 years of age. Prospective studies with preoperative and postoperative imaging would assist in determining the timing of brain injury. *(J Pediatr 2019;212:93-101)*.

With improvements and advances in surgical techniques, antenatal care, and neonatal care over the last 60 years, the mortality rate from neonatal surgery has declined from 72% in 1949 to <5% in 2013.[1,2] With improving survival there has been increasing concern about long-term morbidity, with evidence that children are at increased risk of neurodevelopmental impairment after noncardiac surgery.[3-8] A meta-analysis from Stolwijk et al revealed mean cognitive and motor development scores of 0.5 SD and 0.6 SD, respectively, below the expected population average at 1-2 years of age.[3] Cognitive delay, including mild delay, was reported in a median of 23% (range, 3%-56%) of survivors of neonatal surgery, with motor delay evident in a median of 25% (range, 0%-77%).

The etiology of neurodevelopmental impairment in this clinical context remains unclear and is likely to be multifactorial. Alterations in brain development, growth, and injury patterns are possible causes. Brain injury is one of the most common and important complications associated with neonatal surgery for congenital heart disease.[9-12] In this population of neonates, white matter injury is the most frequent finding on cerebral magnetic resonance imaging (MRI). Preoperative abnormalities, including white matter injury, ischemic strokes, and parenchymal hemorrhages, are seen in up to one-third of infants with worsening

3D	3-dimensional
MRI	Magnetic resonance imaging
Bayley-III	Bayley Scales of Infant and Toddler Development, 3rd Edition
CDH	Congenital diaphragmatic hernia
SNAPPE-II	Score for Neonatal Acute Physiology – Perinatal Extension, Version II
PMA	Postmenstrual age
PLIC	Posterior limb of the internal capsule
WMSA	White matter signal abnormality

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Supported by grants from the National Health and Medical Research Council of Australia (Centre of Research Excellence #1060733; Project Grant #1028822; Career Development Fellowship #1141354 [to J.C.]; Senior Research Fellowship #1081288 [to P.A.]), and the Victorian Government's Operational Infrastructure Support Program. M.M. received funding from the Australian Government Research Training Program Scholarship, Neurosciences Victoria Brains and Minds Scholarship, and The Henry and Rachel Ackman Travelling Scholarship. The other authors declare no conflicts of interest.

Portions of this study were presented at the Pediatric Academic Societies annual meeting, May 5-8, 2018, Toronto, Canada and the Perinatal Society of Australia and New Zealand, March 25-28, 2018, Auckland, New Zealand

https://doi.org/10.1016/j.jpeds.2019.05.050

of lesions or development of new lesions in ≤70% of infants postoperatively.[9-13] Brain maturation delay of approximately 1 month is common in this population of term-born infants and may predispose these children to subsequent brain injury through similar mechanisms to those seen in infants born prematurely.[10,13] Conversely, very little is known about the incidence of brain injury or brain maturity in neonates requiring noncardiac surgery. Stolwijk et al reported an incidence of cerebral MRI abnormalities postoperatively of 63% in neonates, both term and preterm, requiring noncardiac surgery in the first week of life.[14]

The aim of the current study was to compare brain structure at term corrected age and neurodevelopmental outcomes at 2 years of age in infants after noncardiac surgery with a nonsurgical control group. It was hypothesized that the infants who underwent noncardiac surgery would have more brain injury, delayed brain development, and worse neurodevelopment than controls.

Methods

This was a prospective case-control study of newborn infants requiring noncardiac surgery recruited as part of a larger study looking at growth and neurodevelopmental outcomes after neonatal surgery. The sample size for this study was limited by the number of cases and, as a result, was based on feasibility. Recruitment occurred at the Royal Children's Hospital, Melbourne, Australia. Infants born at ≥32 weeks of gestation with a diagnosis of esophageal atresia, congenital diaphragmatic hernia (CDH), or anterior abdominal wall defect were eligible. Exclusion criteria included a known genetic anomaly associated with developmental impairment, anticipated delay of surgery beyond 2 weeks of age, or instances when death was thought to be imminent. The Score for Neonatal Acute Physiology – Perinatal Extension, version II (SNAPPE-II) was used as a measure of illness severity over the first 12 hours of life in the surgical cases.[15] The score provides a number from 0 to a maximum of 162, with the score increasing with worsening illness severity. The UK-World Health Organization preterm growth charts were used to assess growth.[16,17]

Control infants, born at ≥32 weeks of gestation, were matched to surgical cases by sex, gestational age at birth, and postmenstrual age (PMA) at the time of MRI ±2 weeks. Controls were recruited contemporaneously from a nearby perinatal center, the Royal Women's Hospital, and were part of a prospective longitudinal cohort study investigating the long-term outcomes after moderate and late preterm birth.[18-21] Participants for that study were infants born at 32-36 completed weeks of gestation and a control group of healthy infants born at term (≥37 weeks of gestation) recruited from the postnatal wards.

A questionnaire was given to all families at the time of the MRI to assess various sociodemographic factors. Items from the questionnaire were used to calculate a social risk score for each family. The Social Risk Index assesses 6 aspects of social status, including family structure, education of primary caregiver, occupation of primary income earner, employment status of primary income earner, language spoken at home, and maternal age at birth, which are scored from 0 to 2 for a total score of 0-12.[22,23] Based on the median for the overall risk score, each family were categorized as either lower (score 0-1) or higher social risk (score ≥2).

Ethics approval was obtained from the human research ethics committees in both hospitals. Written informed consent was obtained from the parents of all participants. An interpreter was used if required.

Cerebral MRI

Neonates underwent MRI at 4 weeks' postoperative age or before discharge, whichever happened first. For those born preterm, imaging was carried out at term-equivalent age. All the infants were imaged at a PMA of between 38 and 45 completed weeks. Infants were not specifically anesthetized or sedated for the purpose of the scan. Infants were lightly clothed, swaddled, and placed in a beanbag vacuum fixation device (MedVac; CFI Medical Solutions, Fenton, Michigan), and then placed in the scanner.

Each infant was scanned with a 3 Tesla (T) MRI scan (3T Magnetom Trio Tim; Siemens, Erlangen, Germany) using a 12-channel circular polarized volume extremity coil at Royal Children's Hospital. The following sequences were taken: 3-dimensional (3D) T2-weighted axial images (slice thickness 2.5 mm, repetition time of 5170 milliseconds, echo time of 145 milliseconds, flip angle 9°); 3D T2-weighted sagittal images (slice thickness of 1.6 mm, repetition time of 6240 milliseconds, echo time of 156 milliseconds, flip angle of 120°), and 3D T1-weighted axial images (slice thickness of 0.9 mm, repetition time of 2100 milliseconds, echo time of 3.52 milliseconds, flip angle of 9°). Coronal and sagittal T1-weighted images were reconstructed after acquisition.

MRI Assessments

Each scan was assessed by ≥1 of 4 neonatologists with expertise in neonatal cerebral MRIs who were blinded to PMA at the time of the scan. Assessors of the control infants were blinded to gestational age at birth and perinatal course. Assessors for the surgical patients were blinded to the surgical diagnosis of the patient and the gestational age at birth. Scans were assessed qualitatively for evidence of brain maturation and injury, and quantitatively for measures of brain size using a standardized scoring system previously used for very preterm infants and for moderate to late preterm infants.[20,24,25]

Measures of Brain Size. Biometrics is a tool initially described by Nguyen et al in the very preterm population and has shown good correlation with brain volumes.[24] The metrics were obtained according to methods previously published, including biparietal diameter of the brain and cerebral

cavity, interhemispheric distance, superior extra-axial distance, lateral ventricular width, surface area of the deep gray nuclei, transcerebellar diameter, and corpus callosum measures.[20,24]

Maturation of the Brain. Myelination within the posterior limb of the internal capsule (PLIC) and the degree of cortical folding were used to assess the maturation of brain development. Myelination of the PLIC was assessed on T2-weighted axial images at the level of the foramen of Monro. Myelination was described as one-third complete, two-thirds complete, or fully complete. Myelination of the PLIC was felt to be appropriate for term-corrected (>38 weeks of gestation) if it was two-thirds to fully complete, and myelination of one-third or less was categorized as delayed at ≥38 weeks of gestation.[26]

The presence or absence of the tertiary inferior temporal and tertiary inferior occipital sulci were used to assess gyral maturation. Absence of these gyri was considered to be equivalent to the degree of cortical folding expected at 36-38 weeks of gestation. The absence of secondary inferior temporal and secondary inferior occipital sulci together with the absence of anterior and posterior orbital sulci was considered to be equivalent to the degree of cortical folding expected at 34-36 weeks of gestation.[25]

Measures of Brain Abnormality. Each scan was assessed for the presence of abnormalities in signal intensity, cysts within the white matter, and abnormalities of signal intensity specifically within the deep nuclear gray matter and cerebellum. Signal intensity abnormalities were hyperintense on T1-weighted images and hypointense on T2-weighted images.[25-27]

Global MR Imaging Abnormality Score. A global MR abnormality score was assigned using a technique described by Kidokoro et al incorporating biometrics with modified cutoff measurements previously published from a local cohort.[20,25] The global abnormality scoring system is used to define the nature and extent of regional and global brain abnormalities. The brain is divided into 4 areas—cerebral white matter, cortical gray matter, deep nuclear gray matter, and the cerebellum. Measurement of the size of the lateral ventricles, biparietal diameter, and corpus callosum together with the degree of myelination and presence of cysts or signal abnormality are used to assess the cerebral white matter.

Cortical gray matter is scored by measures of interhemispheric distance, gyral maturation, and the presence of signal abnormalities. Both the deep nuclear gray matter and the cerebellum are assessed using measures of size and the presence of signal abnormalities. The scores in each area are categorized as normal, mild, moderate, or severely abnormal. A global score is calculated by adding the scores from each area, which is then categorized into levels of abnormality as described.

Neurodevelopmental Assessment

Cognition, expressive and receptive language, and gross and fine motor skills were assessed at 2 years of age using the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III) by accredited allied health care professionals. Assessors were not blinded to the surgical conditions. The standardized test norms have a mean of 100 with a SD of 15. Developmental delay was defined as a score of >1 SD below the mean, that is, a score of <85. All survivors were also examined by a pediatrician for signs consistent with cerebral palsy.

Statistical Analyses

Data were analyzed using Stata software version 14 (StataCorp LP, College Station, Texas).[28] Descriptive statistics were applied to describe the overall findings of both groups (cases and controls). Mean (SD) and median (IQR) are reported for the parametric and nonparametric data of continuous variables respectively. Categorical variables are presented as proportions and ORs with 95% CIs. The Student paired *t* test was used to compare differences in continuous variables between matched cases and controls, including brain metrics and neurodevelopmental outcomes. The Wilcoxon rank-sum test was used to compare differences in continuous nonparametric data. Results are presented as mean (SD) along with mean difference and 95% CIs. A *P* value of <.05 was considered statistically significant. The χ^2 test or Fisher exact test were used to compare categorical variables and the χ^2 test for trend when the variables were in ordered categories. ORs (95% CIs) were used to compare binary outcomes between the 2 groups. Linear regression was used to determine the relationship between MRI findings and the composite scores on the Bayley-III, and logistic regression was used to evaluate the relationship between MRI findings and developmental delay. The results were adjusted for confounders, including PMA at the time of imaging and social risk. Results were not corrected for multiple testing because we considered them to be exploratory, and they should be interpreted with caution.

Results

We recruited 54 patients between April 2011 and July 2013 into a larger cohort study investigating neurodevelopmental outcomes in surgical neonates. One-to-one matching with controls was possible in 39 cases. Matching was not possible in 11 cases for whom the cerebral MRI was performed, for various reasons, before a PMA of 38 weeks (2 cases) or after a PMA of 45 completed weeks (9 cases). There was no postoperative MRI performed in 3 cases. Data from the 78 matched patients only were included in the analysis, the characteristics of whom are shown in **Table I**. There was no difference between the surgical cases which could not be matched and those that were matched, apart from PMA at time of MRI (**Table II**; available at www.jpeds.com).

Table I. Participant characteristics

Variables	Surgical cases	Controls	Mean difference/OR (95% CI)	*P* value
Birth weight, kg	2.94 ± 0.69	2.95 ± 0.81	−0.02 (−0.35 to 0.32)	.93
Gestational age at birth in weeks	37.8 ± 2.1 (32.0-40.7)	37.8 ± 2.5 (32.6-41.7)	0.1 (−1.0 to 1.11)	.91
PMA at time of MRI in weeks	41.6 ± 1.9 (38.1-45.9)	41.5 ± 1.5 (38.9-45)	0.1 (−0.7 to 0.9)	.82
Male	23 (59)	23 (59)	1.0 (0.4 to 2.7)	.99
Small for gestational age*	5 (13)	6 (15)	1.2 (0.3 to 5.6)	.74
SNAPPE-II score	5 [0-17] (0-55)			
Esophageal atresia	0 [0-5]			
CDH	25.5 [10.5-35.5]			
Abdominal wall defect	6 [0-17]			
Birth head circumference z-score†,‡	0.5 (1.3)	−0.3 (1.1)	0.7 (−0.0 to 1.4)	.05
MRI head circumference z-score†,§	−0.1 (1.1)	0.6 (1.0)	−0.7 (−1.2 to −0.2)	.01
Maternal age in years	29.3 ± 5.6	34.1 ± 4.5	−4.8 (−7.2 to −2.5)	<.01
Maternal tertiary education¶	20 (53)	28 (72)	0.4 (0.1 to 1.2)	.08
Higher social risk**	16 (44)	13 (33)	1.6 (0.6 to 4.5)	.32

Values are mean ± SD, median [IQR] (range), or number (%) unless otherwise indicated.
*Small for gestational age was defined as a birth weight of less than the 10th percentile (z-score of <−1.28).
†The z-scores were calculated using UK-World Health Organization preterm charts.
‡Thirty surgical cases and 20 controls had head circumference measured at birth.
§Thirty-two surgical cases and 39 controls had head circumference measured at time of MRI.
¶Thirty-eight surgical cases and 39 controls had maternal education recorded.
**Thirty-six surgical cases and 39 controls had complete data to calculate social risk.

Of the 39 surgical cases, 12 had esophageal atresia, 8 had a CDH, and 19 had an abdominal wall defect. The median age at time of surgery was 17 hours (IQR, 5.6-40.0 hours). Infants with CDH were operated on average on day 4 of life and the other 2 groups were generally repaired day 1 of life ($P < .01$). The median duration of surgery was 135 minutes (IQR, 75-180 minutes). Inhalational gas, generally sevoflurane, was used for anesthesia in 79% of participants, including 21% who also received propofol. One participant received propofol alone for anesthesia and another received local anesthesia. Six participants had surgery performed using muscle relaxation and opiates alone. Morphine and/or fentanyl were the opiates used for analgesia. Pancuronium, suxamethonium, and atracurium were the muscle relaxant agents used during surgery. Two participants were on a midazolam infusion for sedation before surgery and this was continued throughout the procedure. Neonates with a diagnosis of CDH had higher SNAPPE-II scores than those with a diagnosis of esophageal atresia or abdominal wall defect ($P < .01$) and were ventilated for a longer period of time ($P < .01$). However, there was no difference in the average length of hospital stay ($P = .532$).

Mothers of the surgical participants were younger than the mothers of the control participants. Rates of maternal tertiary education were higher in the control group. Social risk was similar between groups.

Brain Imaging

MRI brain for all infants was performed at a median age of 25.5 days (IQR, 16-33) days. A small number of scans were degraded by motion artefact. Coronal images were suitable for scoring in 38 of 39 case-control pairs, and sagittal images were suitable for scoring in 37 of 39 case-control pairs. Axial images were available in all 39 pairs. Cerebellar images were degraded in one of the surgical participants and the superior extra-axial distance could not be assessed in 1 control participant. Consequently there were 36 case-control pairs that had a complete dataset recorded and therefore could have a global abnormality score assigned.

Brain Maturity and Injury

At term-equivalent age, infants who had surgery had a higher rate of delay in cortical folding compared with controls (Table III). There was no difference in the rates of complete myelination of the PLIC between the 2 groups. White matter signal abnormalities (WMSAs) were seen more frequently in infants who required surgery compared with the controls. Rates of cysts and hemorrhage were low in both groups.

Measures of Brain Size. Infants who required surgery had smaller biparietal diameters and larger lateral ventricular widths compared with controls (Table III). There was no difference in the size of the cerebellum, deep gray nuclei area, extra-axial spaces, or corpus callosum between the 2 groups.

Global MR Imaging Score

Table III outlines the proportion of infants with normal, mild, moderate, or severely abnormal scores in each of the 4 brain areas together with their overall score. More abnormalities were detected in those who had surgery compared with their matched controls (Table IV). Abnormalities in the cortical gray matter and cerebral white matter accounted for the difference in abnormality scores.

Neurodevelopmental Outcomes

Of the 39 case-control pairs, 2-year follow-up was completed in 35 of the surgical participants and in 37 of the controls at a mean age of 26 months (SD, 2). One participant from the surgical group with esophageal atresia died at 15 months related to a choking episode and 3 were lost to follow-up

Table III. MRI findings and brain measurements

MRI variables	Surgical cases (n = 39)	Controls (n = 39)	OR (95% CI)	Mean difference (95% CI)	*P* value
Delayed gyral maturation, no. (%)	22 (56)	7 (18)	5.92 (1.91 to 19.47)		<.01
Delayed PLIC myelination, no. (%)	12 (31)	11 (28)	1.13 (0.38 to 3.36)		.80
Signal abnormalities, no. (%)					
White matter	8 (21)	1 (3)			.01
Cortical gray matter	1 (3)	0 (0)	9.81 (1.18 to 446)		.31
Deep gray nuclei	0 (0)	1 (3)			.31
Cerebellum*	1 (3)	0 (0)	–	–	.31
Periventricular cysts, no. (%)	1 (3)	0 (0)	–		.31
Hemorrhage, no. (%)					
Any IVH	2 (5)	0 (0)	–		.16
Cerebellar hemorrhage*	1 (2.5)	1 (2.5)	1 (0.01 to 80.5)		.99
Brain BPD* (mm)	83.99 (4.73)	86.16 (4.50)		−2.17 (−4.28 to −0.06)	.04
Cerebral cavity BPD* (mm)	86.77 (5.32)	89.75 (4.58)		−2.98 (−5.25 to −0.71)	.01
Interhemispheric distance* (mm)	1.87 (0.96)	2.18 (0.83)		−0.31 (−0.72 to 0.10)	.13
Right superior extra-axial distance† (mm)	2.45 (1.39)	2.68 (1.28)		−0.23 (−0.85 to 0.40)	.47
Ventricular atrial width* (mm)					
Right	6.26 (1.99)	5.21 (1.11)		1.05 (0.31 to 1.79)	<.01
Left	5.86 (1.82)	4.91 (1.46)		0.96 (0.20 to 1.71)	.01
DGN surface area (mm^2)					
Right	615.12 (61.53)	625.11 (66.83)		−9.99 (−38.96 to 18.98)	.49
Left	610.57 (63.30)	618.18 (59.70)		−7.60 (−35.36 to 20.15)	.59
Corpus callosum† (mm)					
AP length	44.56 (5.88)	43.26 (4.07)		1.30 (−1.04 to 3.64)	.27
Genu	5.34 (1.14)	5.44 (1.22)		−0.10 (−0.65 to 0.44)	.71
Midbody	2.33 (0.48)	2.53 (0.53)		−0.20 (−0.44 to 0.03)	.09
Splenium	3.83 (0.51)	4.11 (0.90)		−0.28 (−0.62 to 0.06)	.10
Transverse cerebellar diameter† (mm)	55.38 (3.54)	56.52 (2.62)		−1.15 (−2.59 to 0.30)	.12

BPD, biparietal diameter; *DGN*, deep gray nuclei; *IVH*, intraventricular hemorrhage (all were minor).
Data are presented as mean (SD) unless otherwise stated.
*Data were available for 38 matched pairs.
†Data were available for 37 matched pairs.

(2 with abdominal wall defect, 1 with esophageal atresia). Two control participants were lost to follow-up. Of the 37 controls who were assessed, one did not complete the language component and another did not complete the motor component. Consequently there were 35 case-control pairs who had cognition assessed and 34 case-control pairs who had language and motor skills assessed.

Controls had higher composite scores in all domains compared with surgical cases (Table V). None of the participants in this study had a diagnosis of cerebral palsy or visual or hearing impairment at 2 years of age. There were higher rates of delay in ≥1 domain in the surgical group (34%) compared with the controls (17%; $P = .10$).

Within the surgical group, infants with CDH had poorer developmental outcomes compared with those with esophageal atresia or abdominal wall defect. Although there was no strong evidence for differences in mean scores between the groups (Table V), compared with the esophageal atresia/

Table IV. Global abnormality score

Variables	Normal	Mild	Moderate	Severe	*P* value*
Global abnormality score (n = 36 pairs)	(Total 0-3)	(Total 4-7)	(Total 8-11)	(Total >12)	
Surgical cases	29 (81)	7 (19)	0	0	<.01
Controls	36 (100)	0	0	0	
White matter abnormality score (n = 37 pairs)	(Total 0-2)	(Total 3-4)	(Total 5-6)	(Total ≥7)	
Surgical cases	31 (84)	6 (16)	0	0	.01
Controls	37 (100)	0 (0)	0	0	
Cortical gray matter abnormality score (n = 38 pairs)	(Total 0)	(Total 1)	(Total 2)	(Total ≥3)	
Surgical cases	17 (45)	18 (47)	2 (5)	1 (3)	<.01
Controls	30 (79)	7 (18)	1 (3)	0	
Deep gray nuclei abnormality score (n = 39 pairs)	(Total 0)	(Total 1)	(Total 2)	(Total ≥3)	
Surgical cases	36 (92)	2 (5)	1 (3)	0	.47
Controls	37 (95)	2 (5)	0	0	
Cerebellar abnormality score (n = 37 pairs)	(Total 0)	(Total 1)	(Total 2)	(Total ≥3)	
Surgical cases	33 (89)	3 (8)	0	1 (3)	.16
Controls	36 (97)	1 (3)	0	0	

Values are number (%).
**P* value from χ^2 for linear trend.

Table V. Bayley-III scores at 24 months

Bayley-III domains	Surgical cases	Controls	Mean difference (95% CI)	*P* value
Cognition (n = 35 pairs)	97.7 (17.2)	104.9 (16.9)	7.1 (–0.9 to 15.2)*	.08
CDH (n = 8)	*96.3 (26.2)*			
Esophageal atresia/abdominal wall defect (n = 27)	*98.1 (14.2)*		*–1.8 (–16.1* to *12.5)*†	*.80*
Language (n = 34 pairs)	94.3 (20.0)	106.8 (20.6)	12.5 (2.7 to 22.4)*	.01
CDH (n = 8)	*84.9 (21.9)*			
Esophageal atresia/abdominal wall defect (n = 27)	*96.6 (18.1)*		*–11.7 (–27.2* to *3.8)*†	*.14*
Motor (n = 34 pairs)	94.7 (12.5)	108.1 (18.7)	13.4 (5.6 to 21.1)*	<.01
CDH (n = 8)	*91.9 (13.1)*			
Esophageal atresia/abdominal wall defect (n = 27)	*94.7 (13.0)*		*–2.8 (–13.5* to *7.9)*†	*.60*

Data presented as mean (SD); the mean difference and *P* values in italics relate to difference between surgical diagnoses.
*Comparing all surgical cases with controls.
†Comparing CDH with esophageal atresia/abdominal wall defect, within the surgical group.

abdominal wall defect group those who had CDH were more likely to have language delay with a composite score of <85 (CDH, 63% [5/8] vs esophageal atresia/abdominal wall defect, 15% [4/27]; OR, 9.6 [95% CI, 1.2-82.6; $P = .02$) and more likely to have cognitive delay with a composite score of <85 at 24 months (CDH, 37% [3/8] vs esophageal atresia/abdominal wall defect, 4% [1/27]; OR, 15.6 [95% CI, 0.9-848.8; $P = .03$]). Rates of motor delay were similar between the groups (CDH, 25% [2/8] vs esophageal atresia/abdominal wall defect, 19% [5/27]; OR, 1.5 [95% CI, 0.1-12.1; $P = .69$]).

Association between Neonatal MRI Findings and Neurodevelopmental Outcome at 2 Years in Surgical Cases and Controls

On univariable analysis increasing extra-axial space measured using the superior extra-axial distance was associated with poorer cognitive and motor composite scores and higher risk of motor delay (**Table VI**; available at www.jpeds.com). Increasing dilatation of the left lateral ventricle was associated with poorer composite scores in all domains and a higher risk of language delay, although the results did not all reach significance. Higher abnormality scores for white matter, cortical gray matter, and global scores were related to poorer performance in all domains of the Bayley-III. On multivariable analysis (adjusted results in **Table VI**), potential confounders including PMA at time of MRI and higher social risk had little effect on the evidence for association between MRI abnormality measures and neurodevelopmental outcomes at 2 years.

Discussion

The results of this study add further weight to the growing evidence that children are at increased risk of developmental delay after neonatal noncardiac surgery.[3,5] Brain injury and altered growth is likely to play a role. This study demonstrates associations of neonatal noncardiac surgery with WMSA, smaller biparietal diameters, and larger lateral ventricular sizes (suggestive of white matter volume loss), worse brain abnormality scores, more maturational delay, delayed cortical folding, and lower developmental score at 2 years of age compared with controls.

Stolwijk et al described a high incidence of mild to moderate brain abnormalities on MRI performed soon after neonatal noncardiac surgery, particularly parenchymal lesions, seen in 63% of a sample of 101 infants.[14] Thirty-six infants with punctate white matter lesions had MRI performed within 10 days of their surgery. Restricted diffusion on diffusion weighted imaging, suggestive of ischemia, was seen in 61% of those infants. This suggests that the injury occurred in the perioperative period. Our study also showed increased rates of WMSA following neonatal noncardiac surgery; however, because the median time the MRI was performed was 21 days (IQR, 16-31 days), the timing of the injury could not be definitively related to the perioperative period.

Brain injury is one of the most common and significant complications associated with neonatal surgery for congenital heart disease. White matter injury is the most common abnormality seen both preoperatively and postoperatively in that high-risk population, followed by ischemic and hemorrhagic injury.[9-13] The common finding of brain maturation delay may predispose these infants to subsequent brain injury through similar mechanisms as those seen in infants born preterm.[10,13] Brain immaturity has been associated with brain injury preoperatively and postoperatively and has also been associated with more severe postoperative brain injury.[9,10] Beca et al showed that brain immaturity rather than brain injury is associated with neurodevelopmental impairment at 2 years of age after neonatal cardiac surgery.[9] The results of our study showed similar findings with delayed gyral maturation associated with language and motor delay at 2 years in both the surgical cases and the controls.

Most of the literature reporting on neuroimaging in infants after noncardiac surgery relates to infants post CDH repair. Hunt et al showed abnormalities on MRI in a small cohort of CDH survivors, none of whom had required extracorporeal membrane oxygenation.[29] There was a predominance of white matter and deep gray matter injury; increased extra-axial fluid and ventriculomegaly were also common. More recent reports of neuroimaging in the newborn period and in the subsequent 2 years from survivors of CDH repair have continued to show abnormalities in ≤90% of cases.[30-36] Cerebral atrophy, as suggested by ventriculomegaly and increased cerebrospinal fluid spaces,

continues to be the most common finding noted on imaging done postoperatively before hospital discharge. Intraventricular hemorrhage is detected in about 20% of cases.

Similar to neonates requiring cardiac surgery, neonates with CDH have been shown to have brain maturational delay.[37] Danzer et al found delayed brain maturation in 37.5% of infants imaged at term, ranging from 2 to 4 weeks. Other abnormalities included periventricular leukomalacia, underdevelopment of the opercula, intracranial hemorrhage, and prominent extra-axial fluid spaces. A proportion of these infants had neurodevelopmental follow-up at a mean age of 14 months (SD, 7 months) using Bayley-III. Composite scores were in the low average to mildly delayed range with mean scores of 91.2 (SD, 14.4) for cognition, 87.1 (SD, 17.2) for language, and 82.3 (SD, 18.7) for motor. Larger extra-axial fluid spaces were associated with lower cognitive scores, whereas brain immaturity correlated with lower language scores and intracranial hemorrhage was associated with lower motor scores.

Similarly, this study explores the associations of neonatal noncardiac surgery with brain size, maturation, and neurodevelopmental outcome at 2 years. Increased extra-axial fluid spaces with increasing left lateral ventricular size on MR imaging in the neonatal period are associated with neurodevelopmental impairment at 2 years of age with lower composite scores in all domains and an increasing risk of developmental delay. An increasing global abnormality score is associated with lower composite scores in the cognitive, language, and motor domains with a trend toward increased cognitive delay. Increasing white matter abnormality scores and cortical gray matter abnormality scores are associated with poorer performance on neurodevelopmental assessment at 2 years of age. Delay in cortical gyral maturation is associated with lower language and motor composite scores.

The strengths of this study include its prospective nature and the use of a structured systematic scoring system to assess brain size and abnormality on MRI, which increases the reliability and reproducibility of the results. The use of matched controls to compare brain size and structure limits confounding factors, such as gestational age at birth and at the time of imaging. It allowed us to assess infants with esophageal atresia and abdominal wall defects who are often born in the late preterm period. Given the many concerns about the underestimation of developmental delay by the Bayley-III, one of the major strengths of this study is the use of a local contemporaneously recruited control group.[38-40] By having a matched control group, we have shown the significant impact noncardiac surgery has on brain maturation, brain size, and neurodevelopmental outcomes at 2 years of age.

Several limitations need to be addressed when interpreting the results. The small sample size decreased the power of the study to find clinically important associations of noncardiac surgery with the various outcomes. Although children in the surgical group had smaller brain biparietal diameters, larger lateral ventricles, delayed gyral maturation, and higher rates of WMSA, with lower composite scores at 2 years of age on Bayley-III, the rates of mild developmental delay did not reach statistical significance. However, we know from other high-risk groups, including those born preterm and those requiring neonatal cardiac surgery, that brain immaturity, white matter injury, and decreased brain volume are associated with subsequent neurodevelopmental impairment both at 2 years and early school age.[9,25,27,41-45] Although brain metrics have been shown to correlate well with brain and cerebrospinal fluid volumes, it is possible that if formal quantitative volumetric analysis had been used we may have found a stronger association between MRI changes and neurodevelopmental outcomes.[24] Assessment of neurodevelopmental outcomes at 2 years of age for the surgical cohort was performed as part of a dedicated neonatal follow-up program. The assessors were not blinded to the diagnosis and clinical course of the surgical participants, which may have introduced some bias, although the assessors were not aware that the follow-up data collected would be used in analysis with MR findings in the postoperative period.

Although attempts were made to recruit a relatively homogeneous group of patients, the rare nature of these conditions meant that 3 simultaneous cohorts were recruited for 1 study to improve the sample size such that, ultimately, the surgical group was heterogeneous with varying levels of illness severity, which increases the potential for confounding. A further limitation of the current study is that none of the infants was scanned before surgery, so any brain abnormalities identified postsurgery cannot be directly attributed to the surgery or anesthesia per se, because other variables associated with the underlying surgical problem may have led to the observed brain abnormalities.

Children after neonatal noncardiac surgery, when assessed using the Bayley-III at 2 years, have composite scores 0.5-0.9 SD lower than matched controls in the domains of cognition, language, and motor. This study has shown that abnormalities seen on neonatal MRI, particularly of white matter and cortical gray matter, are likely to be significant contributors to poorer neurodevelopmental performance at 2 years. When compared with matched controls, infants requiring noncardiac surgery were more likely to have smaller, more immature brains with more abnormalities on MRI imaging at term. Changes on brain MRIs in the newborn period are predictive of subsequent neurodevelopmental impairment.[9,37,44-47] Further larger studies are required to confirm if delayed brain maturation and alterations in brain growth and structure are associated with subsequent neurodevelopmental impairment after noncardiac surgery. Given the low incidence of these surgical conditions, multicenter studies would be required to evaluate single disease entities. Prospective MRI studies using both preoperative and postoperative imaging would assist with

elucidating the timing of brain injury with a view to exploring potential interventions. ■

We thank the following staff members from RCH Melbourne: Miss Elizabeth Perkins, RN, for help with patient recruitment and data management, Mr Michael J. Kean, Dip App Sci, and all the MRI technicians, and Ms Lisa Kelly, B Hlth Sc (OT), and other members of the neurodevelopmental follow-up team.

Submitted for publication Feb 18, 2019; last revision received Apr 18, 2019; accepted May 20, 2019.

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Data Statement

Data sharing statement available at www.jpeds.com.

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Table II. Patient characteristics of all surgical cases

Variables	Unmatched surgical cases (n = 15)	Matched surgical cases (n = 39)	Mean difference/OR (95% CI)	*P* value
Birth weight, kg	2.92 ± 0.63	2.94 ± 0.69	–0.01 (–0.42 to 0.40)	.94
Gestational age at birth in weeks	38.2 ± 2.7 (32.9-41.7)	37.8 ± 2.1 (32.0-40.7)	0.4 (–1.0 to 1.8)	.57
PMA at time of MRI, weeks	47.1 [45.1-47.6] (35.9-51.4)	41.1 [40-43] (38.1-45.9)		<.01
Male	10 (67%)	23 (59%)	1.4 (0.3 to 6.2)	.60
Small for gestational age*	1 (7%)	5 (13%)	0.5 (0 to 5.0)	.52
SNAPPE-II score	19.5 [5-37] (0-59)	5 [0-17] (0-55)		.03
Esophageal atresia (n = 5)	18 (0-21)	0 (0-5)		.18
CDH (n = 8)	27.5 (7.5-51.5)	25.5 (10.5-35.5)		.60
Abdominal wall defect (n = 2)	5 (5-5)	6 (0-17)		.92
Birth head circumference z-score†,‡	0.3 (0.8)	0.5 (1.3)	–0.2 (–1.2 to 0.9)	.75
MRI head circumference z-score†,§	–0.1 (0.7)	–0.1 (1.1)	–0.2 (–0.9 to 0.6)	.68
Maternal age, years	30.3 ± 6.7	29.3 ± 5.6	1.0 (–2.6 to 4.6)	.58
Maternal tertiary education¶	5 (36)	20 (53)	0.5 (0.1 to 2.1)	.28
Higher social risk**	7 (50)	16 (44)	1.3 (0.3 to 5.2)	.92

Values are mean ± SD, median [IQR] (range), or number (%) unless otherwise indicated.
*Small for gestational age was defined as a birth weight less than the 10th percentile (z-score of <–1.28).
†The z-scores were calculated using UK-World Health Organization preterm charts.
‡Seven unmatched and 30 matched had head circumference measured at birth.
§Eleven unmatched and 32 matched surgical cases had head circumference measured at time of MRI.
¶Fourteen unmatched and 38 matched surgical cases had maternal education recorded.
**Thirteen unmatched and 36 matched surgical cases had complete data to calculate social risk.

Table VI. Association between neonatal MRI findings and neurodevelopmental outcome at 2 years

	Cognition score (n = 70)		Language score (n = 68)		Motor score (n = 68)		Cognition delay (n = 70)		Language delay (n = 68)		Motor delay (n = 68)	
Predictors	**β (95% CI)**	***P* value**	**β (95% CI)**	***P* value**	**β (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
RSAD												
Unadjusted	−3.04 (−6.08 to −0.01)	.05	−3.44 (−7.61 to 0.73)	.10	−3.83 (−6.96 to −0.69)	.02	1.24 (0.67 to 2.30)	.49	1.17 (0.74 to 1.86)	.50	1.84 (1.10 to 3.10)	.02
Adjusted*	−3.11 (−5.91 to −0.31)	.03	−3.90 (−7.83 to 0.04)	.05	−3.38 (−6.56 to −0.20)	.04	1.52 (0.76 to 3.03)	.24	1.31 (0.79 to 2.15)	.29	1.77 (1.04 to 3.01)	.04
IHD												
Unadjusted	−3.75 (−8.28 to 0.79)	.10	−3.88 (−9.69 to 1.92)	.19	−3.81 (−8.55 to 0.92)	.11	2.05 (0.82 to 5.14)	.13	1.74 (0.91 to 3.34)	.10	1.96 (0.90 to 4.24)	.09
Adjusted*	−3.95 (−8.05 to 0.16)	.06	−4.55 (−10.00 to 0.91)	.15	−3.30 (−8.05 to 1.44)	.17	2.95 (1.0 to 8.73)	.15	2.09 (1.01 to 4.32)	.05	1.85 (0.85 to 4.05)	.12
Left lateral ventricle size												
Unadjusted	−2.25 (−4.72 to 0.23)	.07	−3.10 (−6.26 to 0.07)	.06	−3.21 (−5.67 to −0.75)	.01	1.43 (0.85 to 2.41)	.18	1.65 (1.11 to 2.44)	.01	1.41 (0.91 to 2.17)	.12
Adjusted*	−1.99 (−4.23 to 0.24)	.08	−2.68 (−5.67 to 0.31)	.08	−3.14 (−5.59 to 0.70)	.01	1.49 (0.82 to 2.69)	.19	1.73 (1.13 to 2.67)	.01	1.43 (0.93 to 2.20)	.11
TCD												
Unadjusted	1.03 (−0.28 to 2.34)	.12	0.04 (−1.70 to 1.78)	.96	0.92 (−0.39 to 2.24)	.17	1.07 (0.79 to 1.45)	.64	1.08 (0.88 to 1.33)	.44	0.77 (0.59 to 0.98)	.04
Adjusted*	0.90 (−0.95 to 2.76)	.34	0.17 (−2.44 to 2.47)	.99	0.96 (−1.07 to 2.99)	.35	1.18 (0.70 to 1.99)	.53	1.02 (0.74 to 1.40)	.91	0.72 (0.50 to 1.04)	.08
Global score												
Unadjusted	−2.67 (−5.07 to −0.27)	.03	−4.22 (−7.16 to −1.28)	.01	−4.24 (−6.49 to −1.99)	<.01	1.32 (0.85 to 2.03)	.22	1.34 (0.97 to 1.85)	.08	1.53 (1.05 to 2.22)	.03
Adjusted*	−2.29 (−4.60 to 0.01)	.05	−4.22 (−7.11 to −1.33)	.01	−4.06 (−6.45 to −1.68)	<.01	1.43 (0.88 to 2.33)	.14	1.45 (1.01 to 2.10)	.04	1.50 (1.01 to 2.23)	.04
White matter												
Unadjusted	−4.29 (−8.22 to −0.36)	.03	−4.29 (−8.22 to −0.36)	.03	−6.70 (−10.47 to −2.93)	<.01	1.31 (0.63 to 2.70)	.47	1.67 (0.98 to 2.83)	.06	1.71 (0.91 to 3.22)	.10
Adjusted*	−3.57 (−7.33 to 0.18)	.06	−7.29 (−11.90, −2.67)	<.01	−6.03 (−10.04 to −2.03)	<.01	1.44 (0.66 to 3.13)	.36	1.86 (1.02 to 3.39)	.04	1.63 (0.83 to 3.21)	.16
CGM												
Unadjusted	−6.38 (−12.4 to 0.65)	.08	−9.72 (−18.49 to −0.95)	.03	−12.18 (−18.89 to −5.47)	<.01	2.70 (0.66 to 11.04)	.17	1.49 (0.55 to 4.04)	.4		.14
Adjusted*	−6.72 (−13.24 to −0.20)	.04	−11.29 (−19.60 to −2.97)	.01	−11.82 (−18.72 to −4.92)	<.01	4.31 (0.89 to 20.85)	.07	1.93 (0.66 to 5.65)	.23	2.16 (0.64 to 7.35)	.22
DGM												
Unadjusted	1.64 (−10.98 to 14.26)	.80	−4.33 (−19.82 to 11.16)	.58	−3.89 (−17.00 to 9.22)	.56	1.83 (0.27 to 12.37)	.54	3.05 (0.66 to 14.02)	.15	2.93 (0.60 to 14.33)	.19
Adjusted*	−0.07 (−11.94 to 11.81)	.99	−3.48 (−18.74 to 11.78)	.65	−2.31 (−14.95 to 10.32)	.72	2.11 (0.28 to 16.22)	.47	2.58 (0.47 to 14.17)	.28	5.18 (0.75 to 35.71)	.10
Cerebellar												
Unadjusted	−4.92 (−14.79 to 4.95)	.32	−3.14 (−15.63 to 9.34)	.62	−6.39 (−16.58 to 3.80)	.22	1.56 (0.35 to 6.94)	.56	0.88 (0.18 to 4.30)	.87	3.27 (0.72 to 14.88)	.13
Adjusted*	−0.24 (−9.68 to 9.21)	.96	1.02 (−11.29 to 13.33)	.87	−7.04 (−17.18 to 3.12)	.17	–	–		–	3.21 (0.61 to 16.73)	.17
Normal gyral maturation												
Unadjusted	5.71 (−2.66 to 14.08)	.18	10.75 (0.41 to 21.09)	.04	13.72 (5.84 to 21.59)	<.01	0.60 (0.11 to 3.21)	.56	0.72 (0.22 to 2.40)	.60	0.35 (0.08 to 1.60)	.17
Adjusted*	5.05 (−3.10 to 13.20)	.22	12.63 (2.38 to 22.88)	.02	13.89 (5.46 to 22.33)	<.01	0.37 (0.05 to 2.66)	.33	0.47 (0.12 to 1.80)	.27	0.41 (0.08 to 2.11)	.29
Normal PLIC myelination												
Unadjusted	3.53 (−5.22 to 12.28)	.42	8.59 (−2.34 to 19.53)	.12	6.49 (−2.22 to 15.20)	.14	2.62 (0.29 to 23.83)	.39	1.15 (0.31 to 4.19)	.83	0.83 (0.18 to 3.84)	.82
Adjusted*	1.91 (−7.51 to 11.32)	.69	12.85 (1.00 to 24.70)	.03	5.81 (−4.51 to 16.13)	.27	2.74 (0.22 to 33.83)	.43	0.62 (0.13 to 2.96)	.55	1.40 (0.23 to 8.48)	.71

B, regression coefficient; *CGM*, cortical gray matter; *DGM*, deep gray matter; *IHD*, interhemispheric distance; *RSAD*, right superior extra-axial distance; *TCD*, transcerebellar diameter.
*Adjusted for PMA at time of MRI and social risk.